Parasympathetic Nervous System
Part II

Dr. Edward JN Ishac

Smith Building, Room 742
eishac@vcu.edu
8-2127  8-2126

Department of Pharmacology and Toxicology
Medical College of Virginia
Campus of Virginia Commonwealth University
Richmond, Virginia, USA

Neurons of the ANS

- Medulla
- Cardiac and smooth muscle, gland cells, nerve terminals
- Sweat glands
- NE α, β
- Cardiac and smooth muscle, gland cells, nerve terminals
- Renal vascular smooth muscle
- Adrenal medulla
- Epi, NE
- Skeletal muscle
- Somatic
- Parasympathetic
- Sympathetic
# Parasympatholytic Agents

- **Antimuscarinic**: eg. atropine  
  - block Ach in parasympathetic effector junctions (muscarinic receptors)

- **Antinicotinic: Ganglia** eg. trimethapan  
  - block Ach in ganglia (both parasympathetic and sympathetic, NN or N1-receptors)

- **Antinicotinic: NMJ** eg. curare, succinylcholine  
  - block Ach in neuromuscular junctions (skeletal muscle relaxants, NM or N2-receptors)

## Anticholinergic Effects on Organ Systems

- **Heart**: tachycardia, ↑ A-V nodal CV (M2-receptors)

- **Vasculature**: no effect, although toxic doses cause pronounced direct vasodilation (red blotches)

- **Smooth muscle**  
  - GI-tract, urinary tract: relaxation, ↓ secretion, ↓ motility  
  - Lung: bronchial relaxation & ↓ bronchial secretions  
  - Eye: mydriatic (sphincter relaxation), cyclopegic (ciliary muscle relaxation)

- **Secretions**  
  - ↓ secretion: dry mouth, dry skin,  
  - ↓ decreased gastric acid secretion

- **CNS**: agitation, delirium, confusion, elderly are more susceptible
Antimuscarinic Agents

- **Belladonna alkaloids:** well absorbed, CNS effects
  - atropine (7-10 d) - “belladonna”
  - homatropine (1-3 d) - iritis
  - scopolamine (3-7 d) - motion sickness

- **Synthetic antimuscarinics**
  - ipratropium (quaternary amine) - asthma
  - pirenzepine (tri-cyclic, M1-selective) - ulcer
  - benztropine - Parkinson’s disease
  - glycopyrolate (quaternary amine)
  - cyclopentolate (tertiary amine)
  - propantheline (quaternary amine)

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**Deadly Nightshade**

Approx 5,000 per yr

- Mainly atropine
- Devil’s apple
- Stink weed
- Devil’s cherries

**Datura**

- Mainly scopolamine & hyoscyamine
- Thorn apple
- Jimson weed
Virginia Beach Officials Investigate Rash of Jimsonweed Poisonings - Jan 2006

- 12 teenagers were diagnosed with Jimsonweed poisonings
- Jimsonweed, also known as thorn apple, stinkweed, and Jamestown weed
- it is sometimes eaten - or made into a tea - and ingested by young people in an attempt to get high
- they displayed symptoms such as combative behavior, dry mouth/thirst, blurred vision hallucinations and elevated body temperature

Other Parasympatholytics

Hemicholinium
- no clinical use
- inhibits uptake of choline into nerve terminal (rate limiting step)
- leads to decreased Ach synthesis

Botulinus toxin
- prevent release of Ach
- contamination of improperly prepared food

Clinical use: facial muscle spasms, strabismus, wrinkles
Botulinum toxin

Inhibits Ach release
Single treatment can last 3-4 months

Facial wrinkles, FDA Approval: Apr 2002

Botulinum toxin - Strabismus
Clinical uses of Antimuscarinic Agents

- respiratory (decrease bronchial secretion) ie. atropine
- asthma ie. ipratropium
- ophthalmologic (mydriasis, cycloplegia) eg. iritis (ie. atropine)
- Parkinson’s disease ie. benztropine
- cardiovascular ie. atropine
- motion sickness ie. scopolamine
- GI disorders (peptic ulcers (pirenzepine), diarrhea)
- pesticide poisoning (malathion) ie. atropine + 2-PAM
- mushroom poisoning (muscarine) ie. atropine
- nerve gases (sarin) ie. atropine + 2-PAM

Toxicity and treatment

- **Toxicity:**
  dry mouth, mydriasis, cycloplegia, tachycardia, hot flushed skin, agitation and delirium.
  
  High concentrations may cause ganglionic-blockade leading to hypotension

- **Treatment:**
  - quaternary cholinesterase inhibitor eg. neostigmine or physostigmine (cns action)
  - for hypotension: sympathomimetics (α-agonist, eg. methoxamine)
Symptoms of Antimuscarinic Toxicity

Belladonna (beautiful lady) poisoning

- mad as a hatter: CNS, delirium
- red as a beet: direct vasodilation
- blind as a bat: cycloplegia
- hot as hell (a hare): ↓sweat, thermoregulation
- dry as a bone: decreased secretions

Pharmacology of the Eye

“The eye is a good example of an organ with multiple ANS functions, controlled by several different autonomic receptors.” (Katzung)

Increased intraocular pressure: Untreated → blindness

Glaucoma:
- Open-angle (wide, chronic) – treated with beta-blockers and other agents
- Closed-angle (narrow-angle) – dilated iris can occlude outflow. Pilocarpine or surgical removal of part of iris (iridectomy)
Glaucoma

Increased intraocular pressure: Untreated $\rightarrow$ blindness

Glaucoma:
- Open angle (wide, chronic) – treated with beta-blockers and other agents
- Closed angle (narrow-angle) – dilated iris can occlude outflow
  Pilocarpine or surgical removal of part of iris (iridectomy)

Glaucoma treatment
1. $\alpha$-Agonist: ↑Outflow
2. M-Agonists: ↑Outflow
3. $\beta$-Blocker: ↓Secretion
4. $\alpha2$-Agonist: ↓Secretion
5. Prostaglandins: ↑Outflow
6. Carbonic acid inhibitors: ↓Secretion

Ach effects on smooth muscle in the eye

Contraction of sphincter muscle $\rightarrow$ miosis

Contraction of ciliary muscle for near vision

\[ \text{ACH: } - \quad \text{ACH: } + \]
Actions on the Eye

FIG. 19

Glaucoma treatment

1. α-Agonist
   ↑ Outflow

2. M-Agonists
   ↑ Outflow

3. β-Blocker
   ↓ Secretion

4. α2-Agonist
   ↓ Secretion

5. Prostaglandins
   ↑ Outflow

6. Carbonic acid inhibitors
   ↓ Secretion

Drugs used in glaucoma

<table>
<thead>
<tr>
<th>Cholinomimetics</th>
<th>Ciliary muscle contraction → opening of trabecular meshwork → ↑ outflow</th>
<th>Topical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocarpine, physostigmine, echothiophate</td>
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</table>

| Alpha Agonists: Unselective: | | |
|-----------------------------| | |
| Epinephrine | ↑ Outflow | Tropical |

| Alpha2-Selective Agonists: | | |
|---------------------------| | |
| Apraclonidine | ↓ Aqueous secretion from the ciliary epithelium | Topical |

| Beta-Blockers: | | |
|----------------| | |
| Timolol, betaxolol, carteolol | ↓ Aqueous secretion from the ciliary epithelium | Topical |

| Diuretics: Carbonic acid inhib. | | |
|-------------------------------| | |
| Acetazolamide, Methazolamide | ↓ Secretion due to lack of HCO₃⁻ | Oral |
| Dorzolamide, Brinzolamide | | |
| Prostaglandins: | | |
| Latanoprost (PGF₂α) | ↑ Outflow | Topical |
Innervation of the iris

Clinical Setting | Drug | Pupillary Response
--- | --- | ---
Normal | Alpha agonist ie. phenylephrine | Dilation (mydriasis)
Normal | Muscarinic agonist ie. pilocarpine | Constriction (miosis) cycloplegia
Normal | Muscarinic antagonist ie. atropine | Mydriasis, cycloplegia
Horner’s syndrome | Cocaine | No dilation
Preganglionic Horner’s | Hydroxyamphetamine | Dilation
Postganglionic Horner’s | Hydroxyamphetamine | No dilation
Adie’s pupil | Pilocarpine | Constriction
Normal | Opioids (oral or intravenous) | Pinpoint pupils
Eye - Horner's Syndrome

Destruction of Sympathetic innervation to the iris
- loss of preganglionic fibers
- loss of postganglionic fibers
- parasympathetic innervation left unopposed

**Horner's Syndrome** (note sagging left eyelid and miosis)

Adie's Pupil & Iritis

**Adie's Pupil**
- Poor light reflex
- Dilated pupil

**Iritis**
- Muscarinic blocker to dilate pupil to prevent attachment to lens.
- Steroid to treat inflammation.

Fig. 12.9  Tonic pupil: the left pupil is dilated compared to the right.

This 31 year old woman had been aware of pupillary asymmetry for some time. She presented with left facial numbness, the aetiology of which was not established. It rapidly resolved. Examination showed a typical left tonic pupil. The triceps and ankle jerks were depressed.
Question 3

The circles represent the size of the pupils of a patient’s right and left eyes, both without treatment and with two different treatments. Which of the following is compatible with the findings shown for the left eye?

A. Blockade of $\alpha$-adrenergic rec.
B. Blockade of $\beta$-adrenergic rec.
C. Blockade of muscarinic rec.
D. Inhibition of cholinesterase
E. Sympathetic denervation


Topical scopolamine drops on pupil diameter and accommodation in the normal human eye. One drop (0.5%) at zero time and 30 min.
## Parasympathetic Summary

<table>
<thead>
<tr>
<th>Agonists</th>
<th>Agents</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Ach</td>
<td>1. heart ⇒ bradycardia, ↓ contractility, ↓ conduction velocity in the AV node</td>
</tr>
<tr>
<td></td>
<td>2. Bethanecol</td>
<td>2. vasculature ⇒ no effect (no cholinergic innervation)</td>
</tr>
<tr>
<td></td>
<td>3. Pilocarpine</td>
<td>3. smooth muscle ⇒ ↑ tone in intestine &amp; bladder, ↓ tone in sphincters</td>
</tr>
<tr>
<td></td>
<td>4. Methacholine</td>
<td>4. eye ⇒ contraction of sphincter (miosis) &amp; ciliary muscle for near vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. exocrine glands ⇒ ↑ sweating (SNS), salivation &amp; gastric acid secretion</td>
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<td></td>
<td>6. CNS effects ⇒ belladonna toxicity (mad as a hatter, red as a beet, blind as a bat, hot as hell)</td>
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<tbody>
<tr>
<td></td>
<td>1. atropine - non-selective, long lasting</td>
<td>1. heart ⇒ tachycardia, ↑ AV node conduction</td>
</tr>
<tr>
<td></td>
<td>2. scopolamine – centrally acting</td>
<td>2. vasculature ⇒ no effect (no cholinergic innervation)</td>
</tr>
<tr>
<td></td>
<td>3. homatropine – shorter acting</td>
<td>3. smooth muscle ⇒ relaxation in GI &amp; urinary</td>
</tr>
<tr>
<td></td>
<td>4. pirenzepine - M1 receptor selective (anti-ulcer)</td>
<td>4. eye ⇒ mydriasis &amp; cycloplegia</td>
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<td></td>
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<td>5. exocrine glands ⇒ dry mouth, dry skin, &amp; ↓ gastric acid secretion</td>
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<td>6. CNS effects ⇒ belladonna toxicity (mad as a hatter, red as a beet, blind as a bat, hot as hell)</td>
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## Acetylcholinesterase Inhibitors

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<th>Rapidly reversible (competitive)</th>
<th>Edrophonium ⇒ used for myasthenia gravis (aka Tensilon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slowly reversible (competing substrate, carboxylates enzyme)</td>
<td>1. Neostigmine ⇒ does not cross BBB; affects skeletal muscle most strongly; used for myasthenia gravis &amp; ileus</td>
</tr>
<tr>
<td></td>
<td>2. Phystostigmine ⇒ crosses BBB, used for glaucoma and for treatment of belladonna poisoning</td>
</tr>
<tr>
<td></td>
<td>3. Pyridostigmine ⇒ used for myasthenia gravis</td>
</tr>
<tr>
<td></td>
<td>4. Ambenonium ⇒ used for myasthenia gravis</td>
</tr>
<tr>
<td></td>
<td>5. Demercarium ⇒ used for glaucoma</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Irreversible or very slowly reversible (phosphorylates enzyme)</th>
<th>Organophosphate insecticides, nerve gases</th>
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<tr>
<td>Organophosphate insecticides, nerve gases</td>
<td>Echothiophate ⇒ used for glaucoma</td>
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Neurons of the ANS

Structure and Physiology of the Autonomic Ganglion

- Ganglionic nicotinic (sympathetic & parasympathetic) - pentamer: 2 distinct subunits (α,β) - α2β3 or α3β2
  - α chains contain the Ach binding sites
  - binding of Ach → opening of ion channel (Na+ in, K+ out)
Structure of the Ganglia

1. N1 fast EPSP
2. M2 slow IPSP
3. M1 slow EPSP
4. Late, slow EPSP
Autocoids, peptides

Ganglionic stimulants

- **Nicotine**
  - tobacco (0.3-20mg, fatal dose, 40mg)
  - metabolized & excreted rapidly
  - ↑ HR, ↑ BP, ↑ respiratory rate

- **Ach, DMPP** (experimental)

- **Lobeline** (tobacco)

- **Insecticides & rodenticide**
  - nicotine is often the effective agent

- **Toxicity**
  - CNS stimulation: convulsions, headache
  - NMJ paralysis: depolarizing blockade
  - hypertension, hypotension, cardiac arrhythmias
  - vomiting, diarrhea, salivation
Treatment of poisoning from ganglionic stimulants

- **Treatment:**
  - vomiting induced for oral ingestion such as insecticides
- **Treatment symptom-directed**
  - muscarinic excess: anticholinergic (atropine)
  - NMJ blockade: mechanical respiration
  - CNS stimulation: anticonvulsant (diazepam)

Ganglionic Blocking Agents

- **Mecamylamine**
  - effective orally, CNS effects
- **Trimethapan**
  - inactive orally
  - used in hypertensive emergency (cns origin)
  - controlled hypotension during surgery
  - short duration of action, 5-10 min, no cns action
- **Toxicity:** hypotension, postural hypotension
- **Treatment:** pressor agent to counter hypotension
### Predominant autonomic nervous system on effector sites

<table>
<thead>
<tr>
<th>Site</th>
<th>Predominant ANS</th>
<th>Effect of Ganglionic Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterioles</td>
<td>Sympathetic</td>
<td>vasodilation, hypotension</td>
</tr>
<tr>
<td>Veins</td>
<td>Sympathetic</td>
<td>vasodilation, ↓venous return, ↓CO</td>
</tr>
<tr>
<td>Heart</td>
<td>Parasympathetic</td>
<td>tachycardia</td>
</tr>
<tr>
<td>Iris</td>
<td>Parasympathetic</td>
<td>mydriasis (dilation)</td>
</tr>
<tr>
<td>Ciliary muscle.</td>
<td>Parasympathetic</td>
<td>cycloplegia (loss of accommodation)</td>
</tr>
<tr>
<td>GI tract</td>
<td>Parasympathetic</td>
<td>↓tone, ↓motility, constipation</td>
</tr>
<tr>
<td>Urinary</td>
<td>Parasympathetic</td>
<td>urinary retention</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>Parasympathetic</td>
<td>xerostomia (dry mouth)</td>
</tr>
<tr>
<td>Sweat glands</td>
<td>Sympathetic</td>
<td>anhidrosis (low sweating)</td>
</tr>
</tbody>
</table>

Note: Ganglia block also high dose nicotine or high dose AchE inhibitors

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**Dr. Ishac, may I be excused my brain is full.**